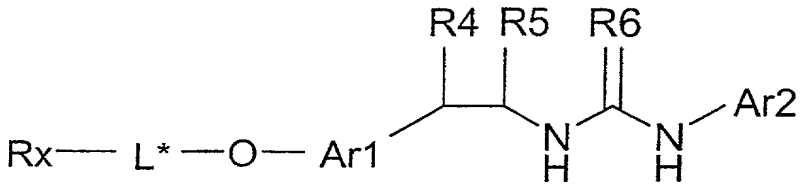
Claims

1 A compound of the formula P1:



P-1

wherein:

Ar1 is an unsaturated, optionally substituted, mono or bicyclic ring structure comprising 0 to 3 hetero atoms selected from S, O and N;

Ar2 is an aromatic, optionally substituted, monocyclic ring structure comprising at least one nitrogen hetero atom and zero to two further hetero atoms selected from S, O and N;

R4 and R5 are independently H or C_3-C_8 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_5 alkoxy, C_1-C_4 alkanoyloxy, C_1-C_4 alkylthio, amino, carboxy, carbamoyl, cyano, halo, hydroxy, aminomethyl, hydroxymethyl, carboxymethyl, or halo substituted C_1-C_6 alkyl mercapto, nitro;

or R4 and R5 join to form a 3 – 6 membered , optionally substituted ring structure;

R6 is O or S;

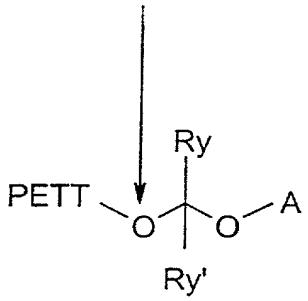
L* is a linker moiety which is ether-, carbonate- or ester-bound to the adjacent oxygen and ester linked to Rx;

Rx is the residue of a natural or unnatural amino acid;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein L* comprises a C_1-C_8 alkyloxy group with an ether linkage to said hydroxy residue.

3. A compound according to claim 2, wherein the alkyloxy group has the formula:



wherein the arrowed oxygen together with PETT is the hydroxy residue of formula I, Ry and Ry' are independently H or C_1-C_3 alkyl and A is the Rx residue or an ester or carbonate bonded intermediate linking moiety to which Rx is esterified.

4 A compound according to claim 3, wherein Ry and Ry' are both hydrogen.

5 A compound according to claim 2 wherein Rx is esterified to the alkyloxy group.

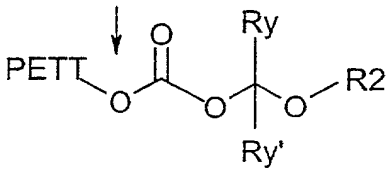
6 A compound according to claim 2 wherein L* further comprises an intermediate linking moiety esterified or carbonate bonded to the alkyloxy group, wherein the intermediate linking moiety possesses an hydroxy group to which Rx is esterified.

7 A compound according to claim 1, wherein L* comprises a carbonyl linkage to said hydroxy residue.

8 A compound according to claim 7, wherein L*' further comprises an intermediate linking moiety possessing an hydroxy group to which Rx is esterified.

9. A compound according to claim 8 wherein the intermediate linking moiety is an optionally branched, optionally monounsaturated alkylenoxy group having 1-3 chain carbons.

10 A compound according to claim 9 wherein L*-Rx has the configuration:



wherein Ry and Ry' are independently H or C_1-C_3 alkyl and PETT together with the arrowed oxygen represents the hydroxy residue of the compound of claim 1.

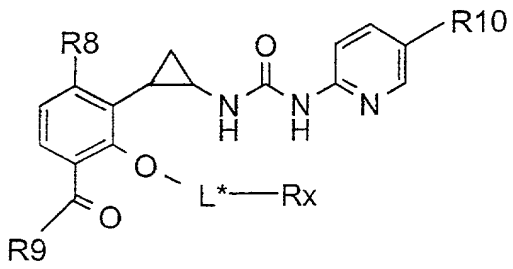
11 A compound according to claim 10, wherein Ry and Ry' are both hydrogen.

12 A compound according to claim 1, wherein Rx is derived from an aliphatic amino acid selected from alanine, leucine, isoleucine, tertiary leucine and valine.

13 A compound according to claim 12 wherein Rx is a derivative of an L-amino acid.

14 A compound according to claim 13 wherein Rx is a derivative of L-valine or L-isoleucine.

15. A compound according to claim 1, with the formula P2



wherein

R8 is halo;

R9 is C_1-C_3 alkyl;

R10 is halo or cyano.

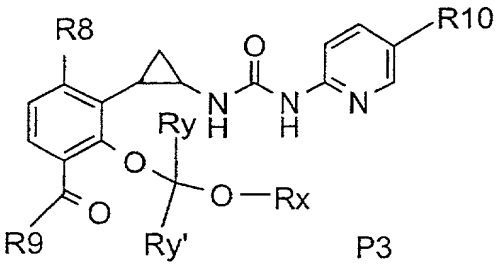
16 A compound according to claim 15, wherein R8 is fluoro.

17 A compound according to claim 15, wherein R9 is ethyl.

18 A compound according to claim 15, wherein R10 is cyano.

19 A compound according to claim 15, comprising at least 90% enantiomerically pure 1S 2S *cis* cyclopropyl configuration.

20 A compound according to claim 15, with the formula P3



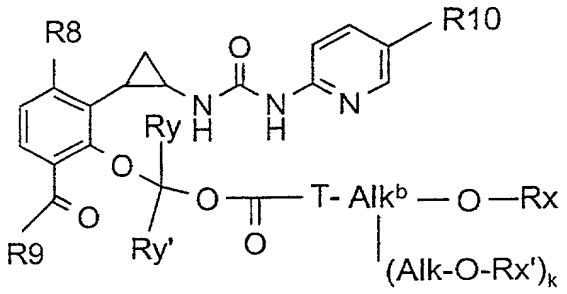
wherein

Ry and Ry' are independently H or C_{1-3} alkyl.

21 A compound according to claim 20, denoted:

(1S, 2S)-N-[*cis*-2-(6-fluoro, 2-(L-valyloxymethyloxy), 3-propionylphenyl)-cyclopropyl]-N'-(5-cyanopyrid-2-yl)-urea or (1S, 2S)-N-[*cis*-2-(6-fluoro, 2-(L-isoleucyloxymethyloxy), 3-propionylphenyl)-cyclopropyl]-N'-(5-bromopyrid-2-yl)-urea.

22 A compound according to claim 15 with the formula:



wherein

Alk^b is an optionally branched, optionally unsaturated C_{1-6} alkyl,

Alk is C_{1-6} alkyl,

T is a bond or -O-

Rx' is the ester residue of a natural or unnatural amino acid, which may be the same or different to Rx;

and k is 0 or 1.

23 A compound according to claim 22, wherein Ry and Ry' are each H.

24 A compound according to claim 22, wherein R_2 is derived from L-valyl or L-isoleucyl.

25 A compound according to claim 22, wherein T is -O-.

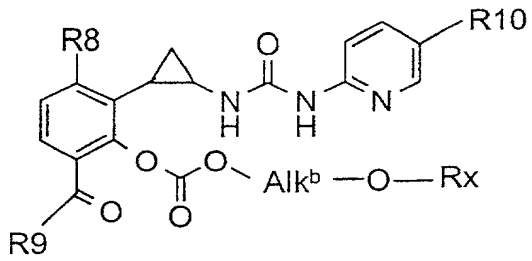
26 A compound according to claim 22, wherein T is a bond.

27 A compound according to claim 22, wherein Alk^b is 1,1 dimethylethylene, 2,2-dimethylethylene, propylene or butylene.

28 A compound according to claim 22 wherein k is 0.

29 A compound according to claim 22 denoted
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-valyloxy-2-(oxycarbonylmethoxy)propyl)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-isoleucyloxy-2-(oxycarbonylmethoxy) propyl)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-valyloxy-2-(oxycarbonylmethoxy)propyl)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(1,3-bis-L-isoleucyloxy-2-(oxycarbonylmethoxy) propyl)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-valyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea,
(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-isoleucyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-cyanopyridyl)] urea,
(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-valyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-bromopyridyl)] urea,
(1S, 2S)-N-{*cis*-2-[6-fluoro-2-(2-(L-isoleucyloxy)-ethoxycarbonyloxymethyloxy)-3-propionylphenyl)]cyclopropyl}-N'-[2-(5-bromocyanopyridyl)] urea,

30 A compound according to claim 10 with the formula



wherein Alk^b is optionally branched, optionally monounsaturated C_1-C_6 alkyl.

31 A compound according to claim 30, wherein Alk^b is methylene or , ethylene.

32 A compound according to claim 30 denoted
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-valyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-isoleucyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-valyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-isoleucyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(2-(L-valyloxy)ethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(2-(L-isoleucyloxy)ethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(2-(L-valyloxy)ethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(2-L-isoleucyloxy)ethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(3-(L-valyloxy)propoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(3-(L-isoleucyloxy)propoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(3-(L-valyloxy)propoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(3-(L-isoleucyloxy)propoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(4-(L-valyloxy)butoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(4-(L-isoleucyloxy)butoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea,

(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(4-(L-valyloxy)butoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
(1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(4-(L-isoleucyloxy)butoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-bromopyridyl)]urea,
or a pharmaceutically acceptable salt thereof.

33. A compound according to claim 32 denoted (1*S*,2*S*)-N-[*cis*-2-(6-fluoro-2-(L-valyloxymethoxycarbonyloxy)-3-propionylphenyl)cyclopropyl]-N'-[2-(5-cyanopyridyl)]urea or a pharmaceutically acceptable salt thereof.

34 A pharmaceutical composition comprising a compound as claimed in claim 1 and a pharmaceutically acceptable carrier therefor.

35. A pharmaceutical composition according to claim 34, further comprising one to three additional antivirals selected from AZT, ddI, ddC, D4T, 3TC, DAPD, abacavir, adefovir, adefovir dipivoxil, bis-POC-PMPA, emtricitabine, tamociclovir (H2G), valtamociclovir stearate (MIV-606), hydroxyurea, Hoechst-Bayer HBY 097, foscarnet (PFA), efavirenz, trovirdine, nevirapine, delaviridine, emivirine, DMP-450, loviride, ritonavir, ABT 378, saquinavir, indinavir, amprenavir (Vertex VX 478) and nelfinavir.

36 A compound as claimed in claim 1, for use in therapy.

37 Use of a compound as claimed in claim 1 in the preparation of a medicament for the treatment or prophylaxis of HIV infection.

38 A method for the treatment or prophylaxis of HIV in a subject in need thereof comprising the administration of an effective amount of a compound as defined in claim 1 to the subject.